Model Psychoses Induced by LSD-25 in Normals

I. Psychophysiological Investigations, with Special Reference to the Mechanism of the Paranoid Reaction

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INTRODUCTION

Experimental psychosis has a long history. It might have started with the administration of Cannabis indica boiling in wine to the ancient Hun warriors, resulting in mental obfuscation, as they were prepared for surgery because of wounds sustained in battle. Scientific experimental psychiatry began toward the end of the last century, in the Kraepelinian era—when the organic theory of psychoses was in its fullest vogue. Beringer's experiments with mescaline [1] marked a milestone in research in that many of the symptoms induced were highly similar to those encountered in schizophrenia and the drug seemed to have had a selective affinity for the brain. The discovery of LSD-25* by Stoll and Hoffmann [2] was an even more exciting event, because the drug worked similarly in infinitesimal-trace amounts. Stoll [3] (1947) suggested the pharmacological designation *Phantastium* for this substance, and he classified the resultant model psychosis as that of the acute exogenous reaction type. Such psychoses are said to exaggerate and caricature the underlying personality of the subject.

Some toxic-organic psychoses, however, have some symptoms all their own. Thus, regardless of the personality structure, the "perception" of moving small animals, in abundance and of vivid coloring, is the stereotype feature of delirium tremens, and confabulations filling in the memory gaps is characteristic of Korsakoff syndrome as part of a cerebral metabolic deficiency state associated with specific involvements in the brain. Those who aver that all psychoses have a biological basis were for a long time on the lookout for a broader foundation, and the drug-induced models were quickly incorporated in this search. No biological theory of psychosis, however, can be held valid if it fails to identify the anatomical area involved or the physiological and biochemical mechanism responsible for dysfunction. The discussion that follows clearly demonstates how very far psychiatry is from the biological theory; it will attempt to summarize the ever-increasing pieces of a theoretical mosaic which represent contributions from many related disciplines, such as psychiatry, psychology, clinical neurology, neurophysiology, neuropathology, biochemistry, neuropharmacology, neurosurgery, and biophysics. Finally, a few working theories will be submitted for critical analysis.

There are excellent surveys available in the literature on the effects of LSD-25 on

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Received for publication July 19, 1955.

Aided by the Margaret Mayer Research Fund.

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* *d*-Lysergic acid diethylamide is a semisynthetic derivative obtained by condensation of *d*-lysergic acid, an extract of ergot, with diethylamine, a secondary amine. LSD-25 thus belongs to the ergonovine group. The drug was supplied to us by Prof. E. Rothlin, of the Sandoz Pharmaceutical Co., Basel, Switzerland, and its West Coast representative, Mr. Harry Althouse, San Francisco.

normal,† psychotic,‡ and neurotic § humans and on animals. It might be important to point out the differences among the authors in their approach to the study of the effects of this drug. Since the original publication of Stoll (1947) many authors have more or less completely confirmed his findings, employing mostly subjects trained in the biological sciences, and through self-experimentation. Some of the salient features of this intoxication become quickly obvious to even the untrained observer, who, while maintaining a state of self-scrutiny and detachment, is quick to point out particularly his perceptual anomalies. The majority of changes, however, strangely enough, first become noticeable only upon questioning, and it is then that the wide range of variation from one experimental sample to another becomes clear. Self-scrutiny varies in degree from one person to another, and the meaning of the test is conceivably different to each one; even so, the richness of the description and the very difficulty in trying to report often vague changes of the mind itself are distinguishing features of the LSD effect.

It would appear, therefore, of value to relate the personality structure of the subject to his LSD state. One suspects that differences in reaction to the drug might depend partly on the scientific sophistication of the subject, which could account for some of the discrepancies found in the literature as one tries to reconcile the various descriptions. Abramson [23] even called attention to the element of suggestibility of the subject and to the suggestive influence of the investigator, for which there appeared to be a good deal of evidence in the present series.

SELECTION OF MATERIAL

LSD-25 was administered to 25 presumably normal subjects, none of whom, to our best knowledge and in their own admission, suffered from any psychiatric disturbance. The age level varied from 20 to 35 years, and by profession they were classified as follows: four students in physiology, three students in psychology, one medical student, one graduate in theology, six actresses in television, one insurance salesman, one physicist, one car salesman, one ski instructor, two housewives, one grammar school teacher, one girl without any occupation, one filling station attendant, and one laboratory attendant. There were 17 men and 8 women.

At the beginning of our experiments, in the summer of 1951, LSD-25 was generally unknown to the public—in fact, even to many in the psychiatric professions. In the selection of our cases, therefore, we did not have the problem of overcoming artificial prejudices; on the other hand, a great deal more explanation was necessary in convincing the subjects to submit to the test than was the case later on, when several reports appeared, not only in medical journals but in magazines and newspapers, about the strange effects of this drug. Selection of the candidates was done with extreme care.

Usually a prospect was approached by one member of the team, who told him that scientific investigation of the effect of certain drugs on the working mechanism of the mind was in progress at our university. We were in need of volunteers who were considered normal. As a result of the ingestion of a tasteless and harmless liquid, they were going to experience something akin to alcoholic intoxication. They would be required to cooperate in describing whatever changes occurred; they would lie comfortably on a cot; they would be fed lunch at a certain time, and transportation would be provided to and from the place where these experiments were to take place. They were reassured that disturbing after-effects were not expected, that in all probability they would be free to do whatever they wished the evening of these experiments, and that self-scrutiny and insight would never be lost at any time.‖

Only in two instances were our requests turned down because of fear. Three other candidates tried to get out of the experiments by giving all kinds of excuses, which, while quite plausible, left us to suspect that they were covering up their fears. No attempt was made to insist beyond this point.

As a general rule, most of the subjects were quite satisfied, interested, and even delighted by what went on, and, judging from their eagerness in trying to line up for subsequent control tests, it appeared that they were very intrigued about the outcome of the test. Some of them later asked to read the verbatim transcription of the experiment in order to satisfy this curiosity, also because exact recollection of the happenings was often obscure. They related occasionally during the experiment that they felt uncomfortable, anxious, or scared, but in retrospect they were quick to point out that they never regretted having undergone this experiment. The feeling was general that most subjects of this series considered their having undergone this test as a sign of valor. Many were eager to recruit other volunteers, and, at times, it was established that they did so out of sadistic-hostile motivation. Whenever such a subject volunteered to bring a friend, he was closely questioned about his relationship with the prospect. That this was justified was demonstrated by the refusal of a good number of the prospects to comply, indicating, at least on the surface, that the motives of the inducer were doubted or else that his qualification for giving reassurance was not found quite satisfactory. This was admitted by those who, upon our own intervention and repetition of the reassurance, finally consented to come. There was one instance in which a husband was eager to convince his wife to volunteer and it was later established that he harbored a great deal of resentment against her.

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† References 3-12.

‡ References 13 and 15-20.

§ References 14 and 21-25.

‖ By now, several hundred subjects have been submitted to the LSD test, and from personal communication we know of four instances in which the drug precipitated a psychosis, one with a suicidal tendency. The law of averages will inevitably assert itself as the number of experiments increases, but the correctness of the above reassurance essentially prevails.

Six subjects in this series were entertainers on radio and television. They were motivated by an unusual amount of curiosity, and they expressed a wish to read the four-hour-test protocols to one another in a group. They were exhibitionistic in the test, as they were in their own profession. There were more specific motivations to induce others to volunteer. One member of this group contemplated marrying one of our prospects, but he was not able to satisfy his sense of uncertainty about her qualifications. He frankly admitted that he would like to learn something about "what really makes this girl tick."

Whether the senior author of this article was the one who made the first step in trying to recruit volunteers or not, there was never any doubt about his being the leader. The subject's relationship with him during the height of the LSD effect often contained the irrational elements of his relationship to important authority figures, as determined by questioning his friends, relatives, and himself, and by examining the personality tests. In paranoid states the senior author was always the supreme target.

In spite of all the precautions taken to select subjects from the normal population, the control Rorschach test not infrequently brought out latent neurotic, and even schizophrenic, trends which appeared potentially disturbing. It was striking that these were the subjects who were most insistent in urging the author to live up to his promises and to deliver the Rorschach results to them as soon as possible. It would appear to be strongly advisable to be on the lookout for incipient schizophrenia during the process of selection, as the test (in reality a form of stress) could conceivably lead to decompensation.

During the second half of this study, articles appeared in national magazines and in newspapers about experiments with LSD-25 in other institutions. It seemed to us that this preexisting knowledge about LSD-25 had a double effect in our selections. There was an increased amount of curiosity and willingness to experience the bizarre effects of this drug, which were rather sensationally treated in the press, and the prospects required more reassurance about the safety and reliability of these experiments than their earlier colleagues. Fortunately, by that time more than half of our subjects had had their tests, so that we had a certain degree of authority with which to underscore our verbal assurances.

One member of the investigating team was a woman. Only one male subject, who was her acquaintance, showed signs of sexual stimulation toward her at the height of his euphoria. This would confirm the prevailing opinion,[3] debated by few,[20] that sexual drive in the LSD state is, if anything, decreased.

METHOD

The average amount of LSD-25 (given by mouth in distilled water) varied from 30γ to 100γ; but only two subjects had less than 40γ, and the majority received 1γ per kilogram of body weight. The experiments started at noon, the subject having had nothing to eat since breakfast. Lunch, which uniformly consisted of minced meat, bun, and malted milk, was served approximately three hours after the start. The subject would lie comfortably on a padded cot in a Faraday cage lined with a plastic board and provided with a window and a door, which was closed only when the EEG was recorded. Conventional needle electrodes were inserted in the scalp in the frontal, motor, temporal, and parietal-occipital areas and left in place during the experiment. A Grass III eight-channel apparatus was used, and the electrode combinations were both monopolar and bipolar. Each channel was fed into the input of an Offner differential automatic analyzer, which recorded six individual 10-second epochs per channel, and the frequency distribution from each area of the brain was quantitated in the form of a mean histogram on graded paper. The control EEG was recorded during the 10 minutes following the administration of LSD-25, when no effects could be expected, and none were observed or reported by the subject. Only during the few minutes of EEG recording was the subject left alone, though he was still watched through the window.

The first sign of LSD effect consisted of dilatation of the pupil, which occurred from 20 to 30 minutes after ingestion of the drug. Rarely were the subjects conscious of any particular change by that time. Subsequent recordings were made just prior to the administration of the Rorschach tests, one hour after the beginning, and also at two, and even in some instances three, hours after administration of the drug, when the effect reached maximal proportions. In almost every instance, at the end of the experiment (four hours) the EEG was back where it was in the beginning. Rarely, departure from this rigid schedule was made to record the EEG at such times as the subject reported particularly interesting or intensive delusional or hallucinatory phenomena. The effect of single-light-flash stimulation was studied with each sample. This was done in a darkened room with the subject's eyes closed. In some instances air blast through a rubber hose applied to the skin, usually on the leg, operated by an electronic valve, was also used both before and during the LSD effect.

At the height of the intoxication, which usually fell between the second and the third hour, in rapid succession serial seven-digit and test-word retention and recall tests were given, followed by tapping-rate determination of both hands. Tendon reflexes and coordination were tested according to a routine neurological survey of the central nervous system, in turn followed by a two-line writing test and a drawing test that was supposed to gauge ability to judge distance and parallelism and to draw circles. Remote and recent memory was tested in the conventional manner before and during the LSD effect. All these tests were finally repeated several weeks later, when the control Rorschach test was administered.

Throughout the four hours of testing, as nearly complete silence prevailed in the room as was possible. Movements of the members of the team in the neighboring rooms were reduced to an unavoidable minimum. The few standard auditory stimuli consisted of the monotonous drone of the paper drive of the EEG machine, the periodic clicking of the automatic analyzer, and the chimes of a nearby church at 15-minute intervals. All of these played a role and were commented upon during the experiments. In the hypomanic phase, the features of the examiner (at the time only one was in the cage), his clothes, pencil, and paper, were all included in the flighty, distracted verbalization of the subject. A Magnascriber wire recorder was set up in the neighboring room, with remote control and microphone attachments inside the cage. Not only the individual productions but also everything pertinent to the experiment was dictated into the sound track, and all the statements were time-marked. Whenever EEG recording was done simultaneously with the subject's description of his delusions and hallucinations, time markers were made on the EEG paper. The transcription was a phonetic one; not only were the patient's exact productions reproduced faithfully, but even his moanings and grunts were transcribed with as great a fidelity as was possible. Silences and hesitancy were marked on the transcription with dots.

It was felt that a compromise had to be reached between limiting the stimuli to the unavoidable minimum, keeping the environment as constant as possible, even though our set-up might have suffered from the impossibility of testing gait, station, and balance, and the possible distracting effects of objects and personnel that were outside the subject's visual field, under the conditions stated above. After the volunteers were taken home, they were invited to describe on paper whatever possible late effects the drug may have had upon them, but only in two instances were prolonged after-effects of significance reported. These experiments were done on Saturday, and no one was warned to change his usual plan for weekend activity. The subjects were guarded, however, from indulging in excessive amounts of alcohol, which was arbitrarily limited by us to two drinks. Even so, the majority of those who drank alcohol reported that their tolerance on that night was low, and it was exceedingly easy for them to get intoxicated. However, the form that this intoxication took was uniformly the same, namely, irresistible sleepiness. No one suffered major gastrointestinal disturbances either during or for the rest of the day after the experiments. One subject was a linotype setter for a local newspaper, who went to work two hours after the end of the experiment. He reported having heard several complaints of the many mistakes in spelling that he made that night. On the other hand, another subject, a student in physiology, who was preparing for an examination, was able to spend the evening and the following day in hard preparation without experiencing any difficulty in his efforts.

In all but the two first cases, the control Rorschach test was administered (no less than five weeks) after the LSD test. Owing to defects in retention and recall produced by LSD, the control test was less contaminated by the recollection of the drug Rorschach test than was true the other way around.

RESULTS

A. Autonomic Changes

Dilatation of the pupil was present in each case; in fact, it was the first noticeable sign. It occurred on an average within 30 minutes, and in one hour the pupil reached its maximum diameter. Three and a half hours following administration it began to decrease in size, though even after four hours, when most of the experiments were concluded, the pupil was still not back to its original size.

In four cases dilatation was noticed as late as seven hours after the start. In one instance, one pupil was dilated more than the other in a woman who used to complain of migraine headache and in whom a difference in the pupils during the headache had been noted previously.

Increased perspiration, particularly of the hands, was noted in three instances to a great excess and in six instances to a slight extent.

A feeling of general warmth occurred in one instance; it was of a definite, sharp onset and disappeared just as quickly, persisting for three minutes. In one instance a subject complained of a typical bolus hystericus. Five cases reported a mild degree of nausea.

The intensity of the autonomic changes did not seem to depend on the dose, which was maximally 1γ per kilogram.

B. Perceptual Anomalies

1. *Visual Sensations.*—Visual manifestations were most prevalent, as compared with other sensory changes (18 cases). There is no explanation for the comparative sensitivity of the visual system to LSD, though it never reached the predominance of eidetic phenomena described in mescaline-induced states. There was certainly no correlation with the high alpha index on the EEG, which some authors have related to great visual imagery in thinking.

Commonest were illusions, particularly noticeable with the eyes closed, of which examples are given.

> Bright yellow coils that seem to jiggle like the lines of a poorly functioning television screen. These later on changed into a multicolored, painted turtle, with the colors flowing into one another rapidly.
>
> Black slivers, in the shape of a diamond, the angles of which disappeared when someone clapped his hand close to the subject's ear.
>
> In another case, light manual pressure over one eye caused a black-and-blue-colored, giant bug to appear in that eye, which quickly changed into multicolored flutes, then just as quickly into a spiral staircase, then into modern windows looking out on a pool and a house with the San Francisco Bay Bridge, with the rising sun behind it. This subject emphasized the extraordinary precision and vividness particularly of the last picture and insisted that one should let him enjoy this scenery a little while longer.
>
> Another subject first saw Gothic windows with his eyes closed. Later on, however, searchlights appeared in the bottom of his visual field, with the beams directed upward in a vertical direction, making everything around them extremely dark.
>
> Flickering flash bulbs spread out in a horizontal plane, oscillating and then quickly changing into multicolored ribbons, interrupted by spikes spaced at regular intervals.
>
> Primitive masks of various colors with wings on them, changing into angular, crawling, filmy, feathery croppings, like a forest. In this instance, the change from the mask to the forest occurred upon clapping of the hands. At times, the images seen with eyes closed were very simple, like, for instance, gray-colored, muddy-looking curves, which, upon clapping of the hands, became suddenly elongated and then stayed that way.

One interesting feature of this set of symptoms was the fact that Gothic or cathedral windows, which some of the subjects were capable of reproducing with pencil and paper, were reported by seven subjects. Mayer-Gross also noted that under mescaline he had imageries of cathedrals.

> With eyes open, one subject could see a crimson-colored glow around the edges of all kinds of objects placed before his eyes, upon which the light had fallen.

Visual hallucinations with the eyes open were reported by three subjects.

> One subject, with eyes open, saw Mexican peons with sombreros, dancing or hopping around on donkeys.
>
> Another subject saw, in a completely darkened room, light moving very slowly and deliberately from left to right, hitting only the subject's eyes in a cyclic fashion.
>
> A third subject saw geometrical figures, half-purple and half-black in color, coalescing into a goldfish, and the goldfish then would dance on the wall with the hindfins moving rhythmically.

Anomalies of visual perspective, such as micropsia, metamorphopsia, and heteromegalometamorphopsia, were from time to time (usually for short periods) reported by 10 subjects. Some of these visual sensations were quite complex. For instance, one subject saw the cover of *Time* magazine, with eyes open, upon looking on the wall, with the faintly discernible photograph dilating and contracting in size at first, and later on coming out of the red frame and retracting into it in a rhythmic fashion. This he noted to be synchronous with his breathing. By holding his breath, for instance, he was able to hold the image quite close to his eyes.

The quick change-over from one image to another is illustrated by a subject who, at first with eyes closed, saw a stained Gothic window, the green colors of which began to peel off, turning quickly into autumn leaves, and by the time these autumn leaves had fallen to the ground they quickly changed over into peacock feathers, covering the ground in a random fashion.

It was interesting that the emotional reaction described by the subjects to these various strange occurrences varied from one order of sensation to another. Many subjects, up to the time when they were asked to close their eyes and to describe what they had seen, if anything, emphasized that they felt exactly as if they had taken two martinis and they were in no way in a position to detect anything novel about their state of intoxication. The moment they closed their eyes, however, and the above-described illusions appeared, they were quick to point out that this experience was a different one. Their reactions to the extraordinary variety of the illusions and images, whether they were looking upon them with eyes open or closed, was frequently one of exhilaration, and delight in some instances, and they were quite irritated when they felt that the observers would not allow them to continue to be absorbed and insisted on precise description. They would raise their hands and wave the observers away or, in some instances, very annoyedly ask them to be quiet for a minute, complaining that the kaleidoscopic images followed one another with such extraordinary variety that they were not able to give a proper verbal account.

The situation, however, became at times dramatically reversed when the subjects began to report shrinking or dilatation of images, or when walls were "breathing" in and out, or when various multicolored halos appeared around the lighted edges of certain objects placed in front of them. The prevalent emotional reaction now was one of apprehension. They admitted even a reluctance to describe them, and very frequently they had to be coaxed. It seems that dissolution of the familiar landmarks or spatial orientation was upsetting, and sometimes threatening to their reality control.

2. *Auditory Sensations.*—Nine subjects reported transient hyperacusis, and two noted sound reverberations. On the other hand, auditory stimuli frequently had a profound effect on other sensory experiences.

3. *Gustatory Sensations.* — In one case, nausea was associated with a tobacco-like taste in the mouth in a subject who had never smoked, but the clarity suggested an actual hallucination. This appeared after two hours and lasted two minutes; then in another half-hour it returned and lasted for one minute.

In another case, nausea and a metallic taste occurred each time that the subject had visual reverberations.

4. *Vestibular Sensations.*—This term is used because it involves in pure form the subject's relationship to space—reminiscent of, if not identical with, the vestibular aura common in psychomotor seizures.

In one instance a feeling of giddiness occurred, which quickly changed into a feeling of soaring off into space.

There were many visual anomalies with an alteration of perspective associated with feelings of propulsion and retraction—such an anomaly was a mixed visual-vestibular one.

5. *Bodily Sensations.*—Such changes occurred in 17 cases, and the descriptions of these anomalies are noteworthy for their great variety. It should, however, be noted that only rarely were changes spontaneously reported. These came out usually upon questioning, accounting perhaps for the fact that other authors have not reported a similarly high incidence of changes in body sensations.

The commonest occurrence was a difference in the way one part of the body felt as compared with the rest. The following descriptions will be given to indicate the range of abnormalities noted.

"I can't use my left arm, which feels strange; it has a disconnected feeling. It's flexible and it feels more elastic than the other, and it also feels busier. When the light shines on my limbs, the left looks bigger."

"It seems to me that my body feels different depending whether my mouth is open or closed, or whether my legs and arms are crossed or uncrossed. The left arm and leg feel different; their color is different and the right side appears to be more connected to my body. I also have a feeling as if I had a hole in the middle of my forehead."

"Both arms and legs feel detached. The right one more than the left. The left foot appears to be half as long as the right. I am not conscious of my throat between my head and body."

"My teeth feel numb. My right arm feels stronger, and my right eye definitely feels swollen every time that the light shines on it."

"The ulnar half of my left hand feels different, detached, and it gives me the feeling that I could not perform with it as well as with the rest of my arm."

"The right half of my body feels as if it were 6 o'clock in the evening, whereas the left one feels as if I had just gotten up early in the morning."

"I feel numb from my teeth up and it feels as if that small top part of my body would be completely covered by hair."

"The left arm feels numb, pulled into a knot. It appears thin when the light shines on it, more so than the right, and my whole left side is very suggestible. Whatever I think about it, I feel it right away."

"My body feels completely apart from my brain, and, incidentally, this is a very happy feeling. My abdomen feels disconnected from the rest of my body, and when I use my right hand to write with, it feels disconnected."

C. Synesthesiae

This term will be used rather loosely in the text to describe phenomena characterized by one sensory experience influencing another. In 14 cases—as the complexity of these sensory cross influences increased—a paranoid type of schizophrenic reaction occurred, the evolution of which could be followed (and predicted) step by step. Hence, a detailed treatment of these experiences is deemed to be important.

As mentioned before, in every instance hand clapping, or some such noise as that, was able to change invariably the form of the images, and only seldom was it also capable of changing the color. When the kaleidoscopic illusions had sharp angles, hand clapping would smooth out the angles and turn the fingers into curved ones, which then stayed that way for a while. If the subjects happened to see, however, curved images at the time of hand clapping, these never turned into angular ones; but, rather, they began to coalesce and their color change in some cases.

Optic sensations were most commonly influenced by auditory stimuli. It should again be emphasized that the emotional reaction of the subjects to the influence of random noises (including distant church bells) on their visual sensations was not considered disturbing, but when the auditory stimulus was the voice of the inquiring observer, the subjects began for the first time to become anxious, and from this point on usually anxiety increased, as illustrated by the following examples.

The subject (A) saw Mexican peons wearing sombreros on donkeys dancing on the wall, which after a while would vanish, but then the wall would "breathe" in and out at a rather rapid rate, not coinciding with the subject's own rate of respiration. When the observer, at this point, asked her to continue to describe what she was seeing, she began to complain that the examiner's voice was responsible for these changes; that the "breathing" of the wall followed exactly the examiner's voice, high sounds causing the wall quickly to retract and deep ones causing it to advance slowly forward. Random voices in the background were doing the same thing, causing the "breathing" of the wall to speed up and become extremely disorganized, and, at this point, the patient began to complain that the background voices were "talking terrible things about her." This, then, marked the beginning of a frank paranoid reaction, in which the members of the investigating team were placed in the category of "persecutors who have nothing else to do but to drive the subject out of [her] mind." When she was asked if she really believed that this was so, she admitted that she knew perfectly well that this was part of the experiment but she could not dissociate herself from this conviction. Her attitude became one of annoyance and negativism, which persisted during the rest of the experiment.

Another subject reported a series of experiences which started at the precise moment that Card 2 of the Rorschach test was shown to her. This rare case did not proceed, however, to feeling persecuted:

"As I look at this card I see cream-colored, long towers which, whenever I hear the church bell—

like now, for instance—break up into ever so many little towers, but at the same time the color changes from cream to brown. At this moment, the towers coalesce (as you clapped your hand) into brown scrolls, and then everything on this card appears in a light-blue color. Now that you said 'Card #3,' I all of a sudden see music in the card which I can recognize as being a sequence from the "Bald Mountain Suite," but I don't hear the music—I see it in the form of mountain ranges interconnected by iron bridges." (This sort of experience obviously defies description.)

The influence exerted by the examiner's voice on the subject's body sensations likewise caused anxiety, often admitted to with reluctance, and this feeling apparently acted as the precursor of a subsequent reaction of paranoid coloring.

> (Subject B) "I feel that my left arm is strange, disconnected, pliable, and it appears to be busier than the right side. When you talk about these sensations, however, these sensations leave me. I am frightened by the amount of influence that you have on my feelings, and I resent the fact that I am kept here against my will. I resent the fact that I am suggestible; I know you have fouled me up here, and I demand that you give me some ice that I could put in my left hand to get rid of that strange feeling. You are upsetting me by allowing people coming into this room, and they seem to come in only when I am talking. Why isn't there something done about this?"

The same subject had, at the conclusion of the experiment, reported that the left half of his body, including every organ, felt detached and entirely different from the right, as if he had been split into two and put back the wrong way. Even the left hemisphere of his brain felt different than the right. In addition, he had that feeling that up to the hip he had been suspended in a rubber tube. This split feeling persisted for 12 hours after the conclusion of the test, and it reportedly terminated suddenly, when, at that time, during a sexual act with his wife, he experienced an orgasm.

It was a short jump from complaining that the examiner's voice influences vision or illusion or body sensation to the more annoying complaint that the voice presently subjugates thinking and, finally, that the examiner's thoughts control the subject's thinking. Thought control was associated invariably with a hostile, conspiratorial trend.

When frankly persecutory ideas were admitted, the first target was the examiner; later on, however, all members of the team—in fact, everybody present in the room—was included. There has never been any doubt, however, that, of all the members of the investigating personnel, the No. 1 enemy was the senior author.

One subject, for instance, first complained that the interrogating psychologist was purposely irritating him. He then proceeded to admit that people whispering and walking around in the background were likewise in the league with an aim to annoy and upset him. When he was asked, however, how he felt about the senior author, this subject (C) snarled and spat out in space. It thus appeared that when synesthesiae led to ideas of thought control and influence, the referential ideas quickly went over into frank paranoid delusions. Insight, however, was never lost, but for the first time the subject had great difficulty in maintaining a detached objectivity about the experiment.

Another subject first noted that the psychologist's voice exerted an influence upon his thinking as he was presented the Rorschach cards, at which point he stated, using a language that became more and more reminiscent of that encountered in schizophrenia:

> "I feel persecuted. I have no idea what goes on. I don't want to answer. I don't seem to be able to dissociate these cards. The color red means something that is interesting. I do not feel like answering. I already had suspicious feelings when you gave me a milk shake; I was not able to pull out the straw. I suspect some kind of a trick. I have a fear of losing control. I think you all want to confuse me. I resent that I am suggestible and that I can be talked into everything. I am getting fond of these cards the way one gets fond of one's mother. I think I simply learned to hate you all. I resent the way you talk to me; it's just a lot of 'ice cream' talk."

Another subject reported that the left leg felt lighter than the right; it also felt more excitable, and the excitement was directed and provoked by the examiner's questions.

At this point the subject burst out with this:

> "I suspect a trick. I have the feeling that what I say is unimportant and it's not going to be written down. Everything here seems to be up to the psychologist; what he thinks is important will be written down. I feel I am discriminated against."

Another subject admitted anxiety for the first time when he noted that his own words changed the Rorschach picture, and, after he had remained silent for a while, he stated that he was scared to admit this. At this point, while he was protesting against the examiner's allowing such strange influences to prevail, he also said that he was very uncomfortable and that "the place smells as if it would explode any minute."

One subject acted hypomanic and gave 25 to 30 responses to Rorschach Card 5. He then complained of feeling a hole in the middle of his forehead, and that the examiner, while talking, blew the cold air of his breath into this hole, thus influencing the functioning of the subject's brain and his thinking. He suddenly became morose and taciturn, and when the usual lunch was presented to him, he refused to eat. When asked why, he gave a series of excuses. First, he objected to the straw in the milk-shake cup, claiming that it appeared to him about one mile long. Next, he claimed that he was not capable of eating in a lying-down position, even though he was propped up and covered with an oilcloth bib. He then "frankly admitted" that he was not hungry. It was only after the experiment was concluded that he stated the real reason, namely, that he had the feeling that the food was being poisoned. He gave only four responses to Rorschach Card 5, and all the subsequent responses remained under five per card.

In all instances save one, such a reaction was over at least within three and a half hours after the ingestion of the drug. This particular subject (C), one hour after the conclusion of the test, was standing in front of the building participating in a group discussion (not about the test) when the senior author noted that he kept a distance of approximately 6 ft. from the cluster of five people involved in the conversation. When he was asked about this, he came forward by 3 ft., drew an imaginary straight line with the heel of his shoe on the concrete, put the tip of his shoe on top of the line, and claimed that if he would push his foot one inch beyond the line in the direction of the senior author, he would immediately experience the feeling that he "hates [his] guts."

D. Persistence of After-Image

The persistence of the after-image was very markedly increased in 15 instances. This increase coincided with a marked prolongation of the alpha perseveration time (the period during which alpha waves were blocked after visual stimulation). In one instance, the after-image persisted for two minutes. The average increase was 10 seconds. In all but one case it was the positive after-image that persisted. In one case, however, the negative after-image persisted for eight seconds.

E. Distortion of Time Sense

Time sense was found to be distorted in 14 cases. In 5 of these 14 cases time appeared to be elongated. In six cases it was speeded up, and in the rest of the cases it appeared to be slowed down at first and then speeded up to the remainder of the experiment. This cyclic variation could not be correlated with a hypomanic-depressed emotional reaction cycle. Quite a few subjects were able to follow the passage of the time by counting the sound of a bell of a nearby church. When they were asked to give an opinion about the length of time that they had spent in the laboratory, they would say that, even though they knew exactly how much time had elapsed since they came in, it still appeared to them either much longer or much shorter on the basis of their own subjective experience of the duration.

F. Disturbance of Ego Sense

The ego boundaries were disturbed in varying degrees, under various conditions, at various dosages, and this state persisted for various lengths of time. A feeling of depersonalization and estrangement of a vague character was noted in six subjects, while in another seven these disturbances occurred as an elaboration of the changes that interfered with their visual perspective, and, even more frequently, they were connected with anomalies of their bodily sensation. It seemed as if the ego boundaries were very sensitive to such subjective experiences, to which they reacted with anxiety. The subjects complained that when they were left alone they feared "impending dissolution." Two other patients, however, became exhilarated, as a result of their "all-pervading expansion," and insisted on being left alone to enjoy this state of "floating," or "lightness." For short flashes many patients noted tendencies toward dissociation and self-observation, and one subject pictured himself as the statue "Thinker" by Rodin, with his head propped up in his palm, watching himself undergoing the strange reactions. Feeling of impending ego dissolution occurred mostly in subjects who had relatively large doses. In one subject various degrees of this distortion persisted for over 24 hours.

G. Language Changes

Apart from a definite tendency toward playing with words in various ways, sometimes associated with forced laughter, instances of echolalia were common. The most characteristic language change, however, was condensation of words, consisting usually of uniting the first half of one word with the second half of its opposite. Sometimes a simultaneous feeling of opposite impressions was reported—for instance, "I feel as if I were going up and down in the elevator at the same time," or, "I feel as if I were lying down and standing up all at the same time." This sometimes was extended even to the description of images evoked by the Rorschach card—e. g., "I see the south side of a broad-beamed burlesque queen going north and I am standing in front of her."

Many examples of random condensation of words were picked up from the sound track. One example was "mopher," a condensation of mole and gopher. Instances of a tendency toward alliteration were likewise noted, as, for instance, when describing a Rorschach picture, "This looks like the late, lamented esophagus."

In general, the language changes were very similar to those that were reported by several authors, more particularly by Brickner,[38] who studied the tape-recorded production of subjects who were under deep amobarbital (Amytal) sodium narcosis. Condensation and confusion over opposites and over choice between these opposites were not only expressed in language but were openly admitted in the thinking of the subjects. Most of them felt the simultaneous opposite feelings mildly annoying, though these were not limited to paranoid reaction cases.

There were only two subjects who used the typical peripheral circumlocutions noted in amnestic aphasia. The music coming from a Good Humor man's car was described as "church bells on wheels." Another called a cigarette "smoking stick."

H. Motor Symptoms

Twitching of the muscles of the leg was reported in one instance; facial and eyelid twitches, in another instance. Choreiform hand movements were present in one case. Tremor without chill was present in one case; tremor with chill was noted in another instance, but the tremor outlasted for several hours the disappearance of the chill, and it was limited to the upper extremities.

All subjects were tested for reflexes before and during the test. In 10 instances hyperreflexia of a generalized character, without any pathological reflex activity or lateralization, was noted. Left hyperreflexia was noted in two instances. Since these subjects were lying in bed throughout the test, gait and station were not tested.

I. Emotional Reaction

A variety of emotional reactions occurred in every subject, to some extent. Euphoria throughout the experiment was the case in eight subjects, who spent a considerable amount of the time in giggling and in boasting about their wonderful feeling. In only two subjects was depression the prevailing mood throughout. In all the other subjects mood was variable from one time to another, usually starting out with euphoria, forced laughter, and giggling, and turning into anxious preoccupation at the height of the experiment, especially when this was the forerunner of a frank, disturbed, suspicious, paranoid, dysphoric reaction. Anxiety was anticipatory in some; others, however, described the feeling as if their anxiety were an after-reaction to something terrible that had happened to them—as if they had undergone a big scare, which, however, was now over.

Without exception, the subjects who developed paranoid reactions admitted, not during the experiment but later on, that at the height of their reaction they had fear of losing self-control and of becoming violent. Even the euphoric subjects admitted to small annoyances which interfered with their "enjoyment" of their perceptual anomalies, or else they had the feeling that the variety of their subjective experiences were not taken too seriously. One such subject, for instance, resented the fact that his remarks were always written down on the margin of a white sheet of paper. Most of the subjects commented on the extraordinary redundancy of their perceptual anomalies or of their thoughts, and, while they protested that they were trying their best but could not keep up with words in their attempt to describe what they experienced, a few felt sorry for all the people who missed this extraordinary experience.

J. Tapping Rate

The subject's ability to tap at maximum speed with both hands was part of the study. This was recorded on a wire recorder, and measurements were made at the height of action of LSD and compared with the control values. It was found that, on an average, in right-handed persons the tapping rate on the right side was 120 for a 10-second period, as compared with 110 on the left side. The control figures were 90 and 80, respectively. This would indicate, then, an increase in tapping rate while under the influence of LSD. No change in the pattern was noted.

K. Handwriting and Drawing

LSD produced insignificant distortions in handwriting, but ability to judge size, distance, parallelity, and angles in drawing was impaired as compared with the control samples.

L. Retention and Recall

Every subject, at the height of the test, was given 10 test words, with the explanation that the subject's speech was being examined. In 14 instances, only 3 or fewer out of 10 test words were recalled after three minutes. In another six instances, 4 out of 10 words were recalled, which was considered borderline, while in the remainder, of five cases, recall was within the normal limits.

M. Electroencephalographic Changes

In the spring of 1951, when our experiments began, the consensus was that, however pronounced the effect of LSD-25 was on the psyche, the EEG remained normal. In 1952 Delay and associates,[27] however, injected LSD-25 into the veins of rabbits in amounts 25-600 times as large as the oral dose effective in man and reported a complete flattening of the record, with disappearance of the rhythmic elements of the animal's EEG. They, too, felt that in a few human cases the EEG remained unchanged.

The report of our experience with electroencephalography will be divided into several categories.

1. *Effect on Alpha Index* (22 cases).—Alpha index for our purposes is defined as the amount of alpha activity present in 100 seconds of record in a single channel (occipital) free from artifacts. As stated above, on occasions when the subject reported a particularly vivid or unusual hallucination, the EEG was recorded. Inasmuch as the experience described was sometimes anxiety-laden, there occurred, understandably, a more or less complete blocking of the alpha activity and its substitution by desynchronized low-

voltage fast activity. When, however, the alpha index was determined at the time when the drug had its maximal effect and was compared with the control one, a strip of tracing was chosen when the patient was merely lying motionless in a darkened cage, not reporting any hallucination or delusion in particular. It was felt that such a strip would be more nearly representative of the background activity under maximal drug effect.

While the frequency of the background varied within the normal limits, alpha definition was affected in 18 out of 22 cases. Decrease in alpha index (11 cases) was 30% (range 20%-90%). Increase in alpha index (7 cases) was 50% (range 10%-70%).

In those cases in which decrease in the alpha index occurred two patterns were observable. In some cases the reduction of alpha activity was limited to the occipital areas, which remained that way throughout the experiment. More frequently, however, the normally present central (Rolandic) low-voltage beta pattern began to spread until finally the whole cortex became devoid of alpha waves. There was a time when the parietal alpha activity was gone while the occipital areas were still exhibiting synchronized alpha activity. Therefore, it would seem that we were not dealing with a sudden process of desynchronization, such as occurs in visual or mental stimulation—affecting the EEG in toto—as would be expected in anxiety. Rather, there was a gradual spread in the relative displacement of the alpha pattern, much as is seen after intravenous barbital administration, though without the characteristic monorhythmic fast activity seen in the latter.

2. *Abnormal Activity.*—In three cases large (up to 150μv), 6 cps bursts swept through all the leads, in the absence of drowsiness.

3. *Paradoxical Activity.*—Gibbs has described the appearance rather than the blocking of alpha activity in response to light stimulation or opening of the eyes in drowsy subjects. This was seen in four of our cases, but drowsiness here could not be ascertained (Fig. 1).

4. *Response to Single-Light Stimulation.*—Every subject was given 30 single-light stimuli in a darkened room with eyes closed. The perseveration time—the interval between disappearance and reappearance of alpha waves—following the 0.2-second light stimulus was determined before and two hours after the administration of the drug. Perseveration-time average before drug administration was 0.41 second; perseveration-time average after administration was 0.90 second. Alpha blocking was therefore over twofold prolonged. This might tie in with the clinical observation that the time of persistence of after-image was frequently elongated—at times to two minutes.

5. *Deactivation in Response to Hallucination.*—It was known that during the visual hallucinations provoked by mescaline the well-synchronized alpha activity of relaxation was brusquely replaced by a deactivated low-voltage fast pattern. This observation was more than confirmed when working with LSD. In two subjects who had primary visual hallucinations in the right half-field only, the left occipital alpha was absent while the right one was prominent. This ceased immediately with the disappearance of hallucination (Fig. 2).

Delay [27] and others were able to bring back bursts of normal rhythm in the flat, deactivated record of their rabbits under the LSD effect with the intracarotid administration of 40γ/kg. of acetylcholine. This would suggest that the mechanism to account for focal deactivation might be due to regional vasospasm.

6. *Response to Tactile Stimulation.*—In a previous work [34] we reported on the effect of tactile stimulation by graded air blast on the spontaneous electrical activity of the cortex. In some subjects, after a long latency (one second), bursts of fact activity (18-22 cps) appeared for 0.36 second (when the stimulus lasted 0.2 second) bilaterally without desynchronization of the occipital alpha waves. It was thought that this represented

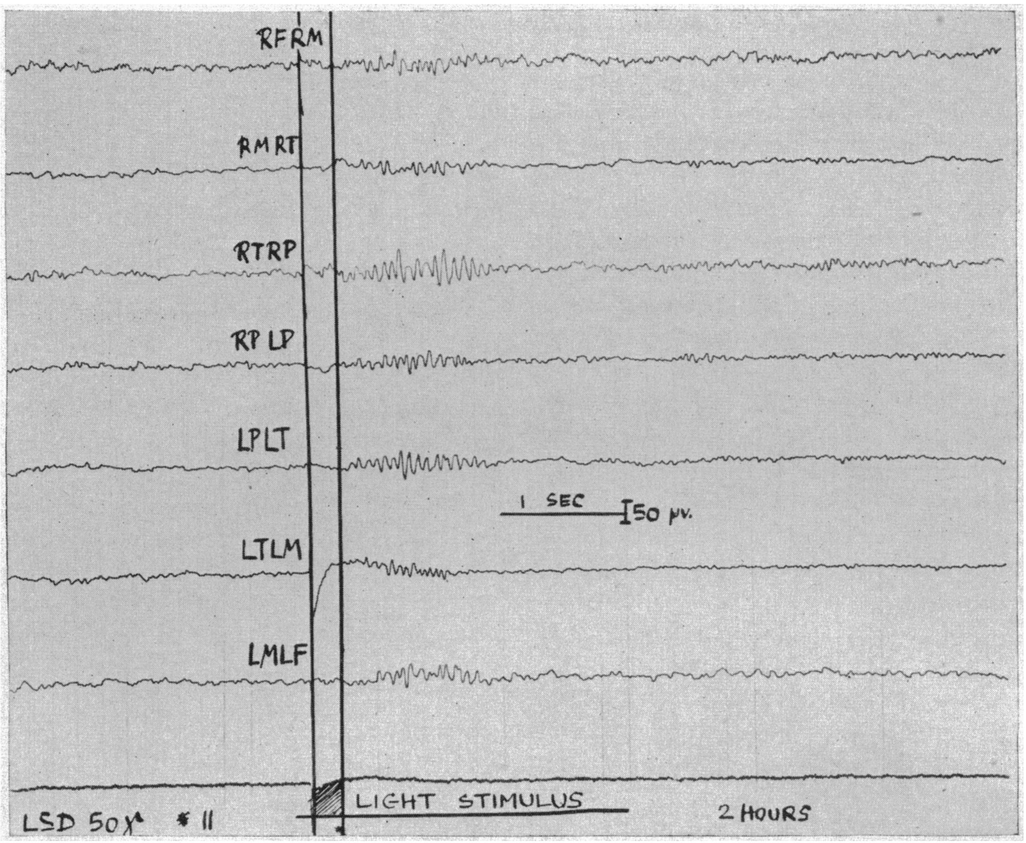
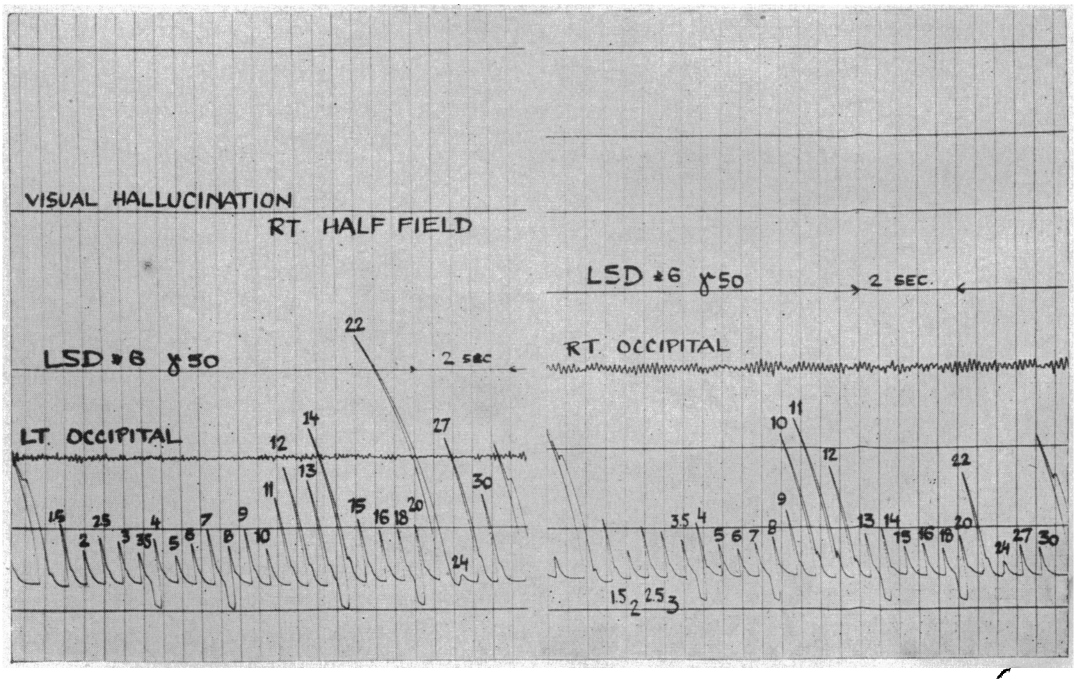


Fig. 1.—In some cases the effect of a single-light-flash stimulation of 0.2 second's duration produces a paradoxical effect, consisting of the sudden return of alpha activity, rather than its blocking, in a nondrowsy subject, whose alpha activity shows reduction at the end of two hours following administration of the drug.

Fig. 2.—Desynchronization of alpha activity in the left occipital area only, coincident with the occurrence of visual hallucination limited to the right half of the visual field.



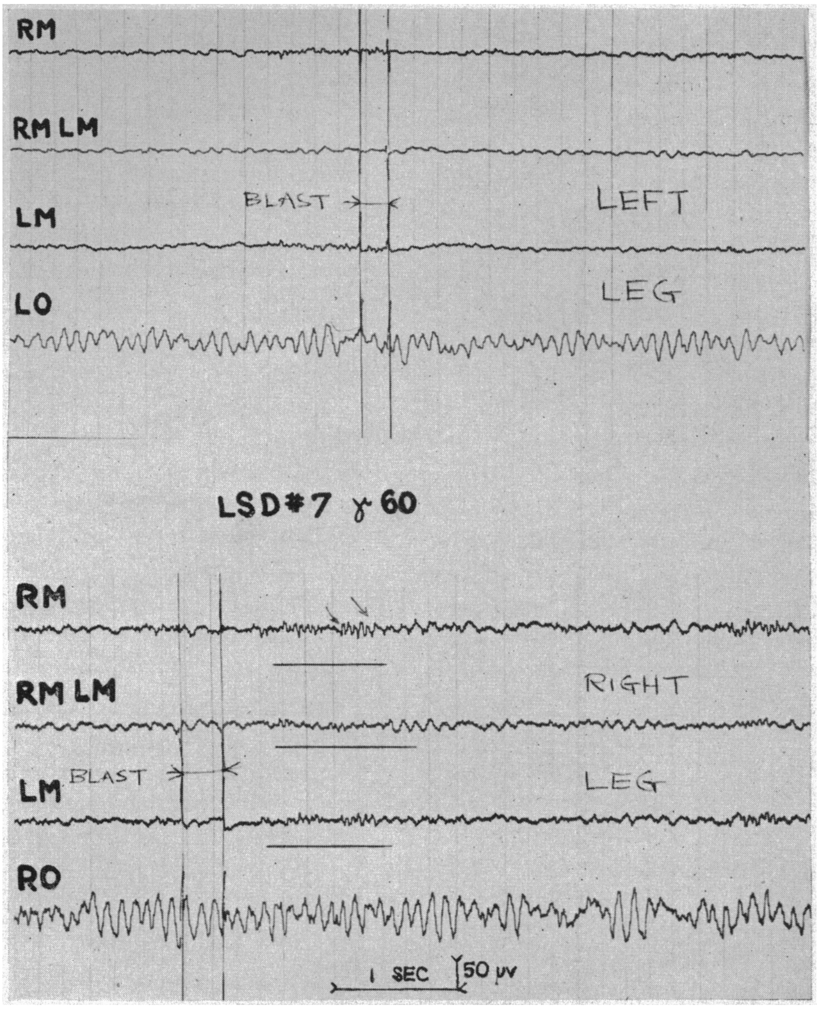


Fig. 3.—Response to tactile stimulation of 0.2 second's duration in a subject who claimed inability to perceive feeling in the left half of his body. Graded air blast applied to the left leg caused no change in the EEG, while the same stimulus of 0.4 second's duration, applied to the right leg (which he was able to feel), produced a rebound, delayed fast burst bilaterally, after a short latency. When this change in body sensation disappeared later, the fast bursts appeared when either leg was stimulated.

a secondary rapid after-discharge and the rebound return of the central beta pattern. Four out of the six subjects originally used for these experiments, when given LSD, developed a delusion of body scheme involving the left side of the body, which they were unable to feel and which "did not belong to them." When the air blast was applied to that side, no change was noted on the EEG on either side. When, however, the tactile stimulation was applied to the uninvolved side, which they did feel, the fast bursts were clearly observable (Fig. 3). This suggests that some blocking takes place in the proprioceptive feedback mechanism that operates in this area, which, as Gastaut has shown, is sensitive to proprioceptive, exteroceptive, and even associational, influences.

Findings such as this tend to emphasize that the EEG is related to the functional organization of the brain and is not merely a side-product of brain activity. More particularly, evidence appears to be present to the effect that the cortex has an ability to distinguish between internal and external stimuli in that it seems to be refractory to external stimulation when it is busy, as it were, for internal consumption.

In conclusion, it appears that LSD produces an alteration in the EEG, with only rare abnormalities outside the alpha range. It is to be expected that the widespread disturbances in mood, feeling tone, alertness, reality testing ability, and perceptional acuity are bound to influence the behavior of the spontaneous electrical activity of the brain, if only in response to various sensory stimuli.

N. Rorschach Tests

All the subjects were tested, but, owing chiefly to the disruptive effect of LSD on test procedures, in only 13 cases was it possible to correlate the drug and control tests. The detailed description of our findings will be described in a later article. In general, there appeared to be potential indices in the control test that could predict a psychotic reaction—the kind of reaction, however, was considerably less precisely foretold. Paranoid and nonparanoid forms of schizophrenia reactions exhibited scores that were not widely differentiated. With one exception, however, the occurrence of complex synesthesiae in the 14 cases that developed paranoid-like reactions acted as a more reliable precursor of the feeling of being persecuted. Our impression was that both psychopathological and pathophysiological factors mattered in the development of the paranoid reaction.

COMMENT

At this point, we are in a position to inquire about the working mechanism of this drug.

A. Biochemical Aspects

There is a general agreement among all the authors who have experimented with LSD-25 that the resultant psychosis model is of the acute exogenous type in the sense of Bonhoffer, as described in 1908. This author assumed in psychoses the existence of a toxic substance arising in an organ that is damaged, or even in the metabolism of the brain itself. He called such toxins "etiological intermediary products." Such an assumption had its starting point in the finding that in certain liver diseases and in some conditions associated with brain damage increased values of certain amino acids were detected in the cerebrospinal fluid. In a variety of psychoses tryptophan could be demonstrated in the spinal fluid with the help of glycoxylic acid as the reagent. The presence of tryptophan is believed to indicate cell damage in the cerebrum.

Blickenstorfer,[37] who has made the most thorough analysis of this problem, postulates that acute exogenous reaction types may occur as a result of starvation, exhaustion, cachexia, fever, and cerebral circulatory embarrassment; and to the toxins due to tissue breakdown must be assigned an important role, besides the parts played by inherited constitution and by psychogenic factors. The question is whether the role of toxins is etiological or pathoplastic.

The infinitesimal amount of LSD sufficient to produce profound selective involvement of the central nervous system is meaningful. If no known measuring method can quantitate the LSD concentration in the body, it is hard to dismiss the possibility that in the psychoses some such substance in likewise small (tracer) amount might be the offending agent.

Fortunately, we do have of late a biological method that can at least affirm the presence—if not measure the amount—of LSD in the body. Witt[26] selected a spider (Zilla-X-notata) as the subject of standardization, because it has a central nervous system that is both complex and simple and presents negligible variation from one to the other. Also, the building of spider webs can be objectivated (photography), and the speed of formation can be recorded. The spider-web test has been used previously for the detection of Pervitin and strychnine. As compared with the effects of another *psychoticum,* such as mescaline, the regularity and symmetry of the angles of the web are pronounced with LSD, and the speed of its formation is increased. The latter factor is attributed to a better utilization of sensory stimulation. The marked differences between mescaline and LSD in their respective effects on the spider suggested to Witt a possible difference in point of pharmacological action, which is all the likelier as the effects of these drugs on the human also present definite differences. The suggestion is obvious that the body fluids of normals and psychotics should be compared as to their effects on the spider, a study which is one of our present projects.

Abramson and Evans[24] recently found a specific psychobiological effect of LSD on the Siamese fighting fish and set up nine criteria with respect to changes in posture and state of consciousness that would permit use of the fish for a biological assay. No mention is made, however, on the effect of other substances on the fish in their preliminary report.

There is general agreement that certain psychotics are relatively resistant to the effects of LSD. Resistance cannot be attributed to the negativism, dissimulative tendency, and fluctuating emotivity of the schizophrenic, for instance—which might interfere with the reporting of LSD changes—since resistance occurs in all forms of psychosis. Those who report on hallucinations are aware of an alien addition to their "customary" hallucinations. One reason for this refractoriness might be the existence of LSD or LSD-like substance in large quantities in the central nervous system of psychotics, so that the addition of a few micrograms of substance is ineffectual. The effective dose is 1γ/kg. for normals and 3γ-6γ/kg. for psychotics.

Reference is made to the presence of tryptophan and like amino acids in the spinal fluid after concussion and other conditions of brain damage.

Tryptophan is a waste product of protein catabolism, and it is incorporated into the formula of LSD-25. Blickenstorfer points out that, while this may be incidental, on the other hand, it may also be considered an indication that LSD somehow appears in human metabolism. It need not be an alien substance. LSD can be partially synthetized out of amino acids, such as tryptophan, two dipeptides, and two tripeptides, which are all normal metabolic products in the human.

There is evidence that some hallucinogens, such as mescaline, form bonds with liver proteins at the time of their maximal effect. Block[33] has shown the inclusion of radioactive mescaline in the liver protein of mice in vivo and adopted the working hypothesis according to which hallucinations found in men originated by mescaline are due to this union of mescaline with body proteins. The moment of appearance and the duration of hallucinations were in agreement with the formation, high-point, and destruction of mescaline-protein. He is of the opinion that it is possible that schizophrenics are suffering from an enduring intoxication by amine proteins, due either to the changes in the amine oxidase system or to the absence of an inhibiting agent. In normals, protection against such protein-amine unions is furnished by the aminoxidase system, an inhibiting factor, and the cell membrane.

Fischer[39] studied the affinity of mescaline, Methedrine, LAE (lysergic acid monoethylamide), and LSD-25 for wool, and found that wool absorbs them in the same ratio as they precipitate model psychoses in normal subjects (500 mg., 100 mg., and 100γ, respectively). All these substances produce initial sympathetic hypertonia, followed by peripheral adrenergic blockage, before psychotic symptoms appear. The higher the initial sympathetic overactivity (stress or the shock phase of the general adaptation syndrome of Selye, or administration of 1 mg. of atropine prior to LSD), the lower the dose of the drug needed to produce a model psychosis. Possibly, persisting stress, causing first sympathetic and later on parasympathetic overactivity, tends to increase the dosage of LSD necessary to produce psychotic symptoms (such as hallucinations) which may serve as an explanation for the resistance of psychotics to doses of LSD effective in normal subjects.

Besides bringing into play the adrenergic factor in the biochemical working mechanism of LSD, this study also points out the analogy between keratin of high sulfur content (wool) and the protein component of certain cell membranes which may be the structural target surface involved in psychoses.

According to Mayer-Gross,[8] LSD-25 seems to interfere with carbohydrate metabolism as well. He found a transitory rise in blood sugar and blood hexose monophosphate in normal subjects subjected to LSD, while the other stages of carbohydrate metabolism were not modified. Although this finding is still awaiting confirmation, this author theorizes that LSD, by an antienzymatic action, interferes with the splitting of sugar to the hexose monophosphate stage. Intravenous injection of 33% dextrose suppressed the LSD effect, and large amounts of glutamic acid likewise acted as an LSD inhibitor. The effect of dextrose is significant in that, if glycogen metabolism is blocked at the hexose monophosphate stage by LSD, and if the psychotic state is related to this, the direct administration of dextrose, which would by-pass the hexose monophosphate chain in order to be utilized, would be expected to have an inhibiting effect on the psychotic symptoms. Optic illusions, feelings of estrangement, euphoria, disturbance in concentration, and various perceptual anomalies did in fact become modified, and, to some extent, they tended to disappear. Since Mayer-Gross and associates did not consider clearly demonstrated a relation in time and severity between the psychological symptoms and the biochemical changes, they repeated their experiments on 13 hospitalized schizophrenics,[41] in view of the fact that such persons have a considerably greater tolerance for the drug and, consequently, they may show only minimal psychological symptoms after the usual oral dose. Eighty micrograms of the drug produced slight psychological effects. Yet hexose monophosphate showed a rise of 1.46 mg. per 100/ml., whereas under control conditions, when water was given, the mean value fell by 1.17 mg. per 100/ml. Mescaline, when given to normals, has produced a psychotic picture rather similar to LSD without a similar rise in the blood hexose monophosphate level. In vitro experiments with tissue brei showed that LSD-25 stimulated the respiration of brain tissue, whereas this was not the case when the tissue was that of the liver of guinea pigs. The authors, therefore, concluded that LSD-25, both in vitro and in vivo, has a sparing effect on hexose monophosphate metabolism, which is greater in the brain than in the liver, and in this respect it reacts unlike mescaline hydrochloride, which has no effect on blood chemistry, even though it is just as capable of producing a psychotic state in normals.

Liddell and Weil-Malherbe [42] have studied the effect of LSD-25 on plasma epinephrine levels and blood sugar concentration in patients suffering from psychoses, as well as in patients with psychoneuroses, and found that there is an initial rise of the epinephrine level, followed by a drop below the starting point and, finally, a secondary rise in epinephrine. The moderate increase of the blood sugar concentration was not considered to be significant.

Rinkel and associates [43] are likewise of the opinion that LSD may interfere with a major enzyme system. They consider the epinephrine system the most important. This is suggested not only by the marked sympathicotonic effect of the drug but by the observations made by Witt,[26] who, when feeding LSD to spiders, noted that each thread was much thinner than those in the control, leading to the speculation that this might be due to the exhaustion of the epinephrine supply of the spider, it being known that the spider web consists almost exclusively of epinephrine. Rinkel recalls the findings in animals by Heirman in 1938, according to whom a metabolite of epinephrine, called adrenoxin, had systemic effects similar to LSD, and an observation of Osmond and Smythies, who, in 1950, reported that an earlier epinephrine metabolite, adrenochrome, known for its hemostatic effects, which showed structural similarly with mescaline, produced dramatic psychotic phenomena in self-experiments. Rinkel was not able to duplicate this observation. However, he is of the opinion that the solution used by the above authors was deteriorating and thereby may have been contaminated by a further epinephrine oxidation product, namely, adrenoxin. He speculates that adrenoxin, a natural metabolite of the decomposition of epinephrine, may be operative in psychosis.

The recent findings of Marrazzi[32] further attempt to enlarge our knowledge about the behavior of epinephrine metabolites and similar substances with respect to their effect on the central nervous system. He found that in cats epinephrine, arterenol, and epinephrine preservatives cause synaptic inhibition, as measured by the decrease in the postsynaptic surface-negative wave, without affecting the presynaptic positive wave. This finding was obtained when stimulating one point of the cat's occipital cortex and recording from the symmetrical point on the other side, which two points are connected through the corpus callosum. He found a similar synaptic inhibition when using such hallucinogens as amphetamine, mescaline, LSD-25, adrenochrome, and serotonin, all showing structural similarity to epinephrine. An incidental observation of his was that serotonin, which was considered by Woolley and Shaw,[31] on the basis of systemic antagonism in animals, as an LSD inhibitor, in his experience had the same effect as LSD on synaptic inhibition. He considered the effect of LSD and other hallucinogens on a group of synapses as typical of a more generalized effect and concluded "that the resulting pattern of over-all activity would be a function of the variations in synaptic thresholds." If further experiments show that LSD affects the occipital cortical synapses differentially, then an explanation may be at hand for some findings which at the moment appear to be puzzling. It is well known that in LSD intoxication visual perceptual anomalies far outweigh the involvement of other sense organs. Alpha blocking following single flashlight stimulation is markedly prolonged in subjects receiving LSD, as compared with control experiments, when the stimulus is visual. Not so, however, when alpha blocking is achieved by other stimulation. Likewise, we have found that persistence of afterimage, when the eyes were closed, very striking, whereas the echo-effect of other sensory modalities proved to be insignificant. The special affinity of LSD for the occipital cortex, which, incidentally, may apply also to mescaline, still has to be confirmed by comparison with the behavior of other synaptic systems.

From the first description of the marked psychotic effects of LSD and the observation that the threshold of psychotics to these drugs is much higher than that of normals, a widespread investigation was directed toward the discovery of LSD antagonists. It has been known that very large doses of barbiturates, or intravenous dextrose, had at least a partial or transitory LSD-blocking effect. In the hands of Hoch, chlorpromazine, as well as a combination of amobarbital sodium and metamphetamine, behaved similarly. Agnew and Hoffer[46] found the effect of intravenous nicotinic acid to be LSD-blocking, while Himwich showed that Frenquil (α-4-piperidyl diphenyl carbinol hydrochloride) has an antagonistic effect on the EEG of rabbits receiving large doses of LSD.¶ Serotonin, with a definite antagonistic effect systemically, failed to overcome the neurological effects of these drugs. Fabing[44] reported on the partially and transitorially antagonistic effect of pipradrol (Meratran) on LSD psychoses in men, while the same drug has a beneficial, euphoria-producing effect in patients who suffer from depression and thus is likely to exert its action on the hypothalamus. Hoff and Arnold[45] found that glutamic acid or succinic acid, which is found in the citric acid cycle, terminated the mental symptoms induced by LSD, and it has also been known that succinic acid temporarily relieved the acute symptoms of schizophrenics. These authors implicate the carbohydrate metabolism in schizophrenia and in conditions induced by LSD, being of the opinion that a disturbance in carbohydrate metabolism may exist in certain circumscribed areas of the brain, possibly in the posterior hypothalamus. It is of interest that patients with damage to this region of the brain were resistant to LSD.

¶ Discussion on LSD Symposium, American Psychiatric Association, Atlantic City, May 12, 1955.

From the available biochemical data, it appears that at the present time the widespread experimental and speculative findings cannot explain the action of LSD satisfactorily. The problem, however, is far greater than the biochemical working mechanism of a drug that is capable of producing psychosis. It ties in with the much more important problem of the biochemical foundation of at least some psychotic states. The ever-greater inclusion of an increasing number of disciplines in psychiatric investigations clearly points to the necessity of integration and synthesis of a great mass of scattered information.

B. Neurophysiological Aspects

Comparison of the LSD state with intoxications produced by other, better-known agents shows similarity and, at the same time, a very definite measure of difference, which puts LSD in a class of its own among the experimental psychotic agents.

All the other agents except mescaline had in common the necessity of using relatively large amounts in order to produce a model psychosis.

In the mescaline state, psychic functions, more than any other, seem to be affected, and the resultant model psychosis appears to be more stereotyped and therefore more predictable. Eidetic phenomena are very much in the foreground as compared with other systems. Catatonic-like schizophrenic states are more prevalent than the other forms. Mood is characterized by dysphoria and anxiety, the latter outlasting by as long a period as one week the administration of the drug. There is even a stereotyped response of the EEG in mescaline intoxication in that the substitution of synchronized alpha rhythm by desynchronized beta activity likewise may go on for several days in fairly good harmony with the state of anxiety which it reflects.

The peculiarity of the LSD model psychosis is the infinitesimal amount of drug necessary to produce a psychosis, which is approximately one-hundredth that of mescaline—an indication of a formidable degree of affinity. Considering the very profound psychotic-like changes produced by LSD, it is surprising how minimal is the interference with intellectual function, a fact which underscores its similarity with the undeteriorated schizophrenic reaction. The LSD psychosis is also noteworthy for its relative sparing of the corticospinal and of the cerebelloextrapyramidal system.

In attempting to localize the possible site of origin of the various psychic manifestations of LSD, on the basis of analogy, most of the symptoms reported are reminiscent of the sensory seizures or psychosensory seizures commonly seen in "psychomotor" epilepsy, and which were reproduced by cortical electrical stimulation by Penfield. This would suggest the primary involvement of the temporal lobe and its connection with the diencephalon. Very few of the phenomena noted in LSD psychosis would have to be localized elsewhere. Thus, for instance, the primary visual hallucinations, delusions, visions, and pareidolias bear a resemblance to the sensory seizures or sensory auras seen in that condition. Micropsia, metamorphopsia, and heteromegalopsia, which are so prominently displayed in the description of LSD psychoses, are elements of temporal lobe seizures, as are kaleidoscopic pictures, vertiginous attacks, and auditory and gustatory, as well as olfactory, perceptual anomalies. Auditory and visual reverberations, feelings of familiarity and unfamiliarity ("I had this test before"), based on both visual and auditory experiences, likewise fall into that category.

In psychomotor epilepsy, it can hardly be implied that the specific cell structures located in the temporal lobe gray matter, in and by themselves, are responsible for the reproduction of these phenomena when electrically stimulated. They merely mark the starting point of an excitation traveling down in a circuit of neuronal chains of various complexity.

Unlike the situation in epileptic phenomena, however—at least when recorded from the intact skull—in LSD psychosis no evidence of synchronized excessive electrical discharge could be detected. It has to be noted, however, that even in psychomotor epilepsy it is not always possible, when recording in this fashion, to find the electrical sign denoting excessive neuronal discharge. Recording directly from subcortical or poorly accessible areas in a human brain (rhinal fissure, undersurface of the temporal lobe) often discloses that, owing to the distance of the recording scalp electrode from the site of origin of the discharge, the spike may not always be picked up, or else, instead of picking up a spike, sharp waves appear, indicating the amount of distortion that takes place when the spike is conducted in distance. The complete absence of any abnormal electrical event in LSD psychosis, even when the site of origin is presumed to be the convexity of the temporal lobe cortex, has been uniformly confirmed. LSD may have a special affinity for these structures, but, because the neurons of these structures are intact, there is no excessive discharge and resultant electrical abnormality. Consequently, the activation and successive involvement of the neuronal chains responsible for the LSD phenomena must have a different mechanism than the one that prevails in seizures. The fact that sometimes these phenomena are enduring, and even rapidly changing back and forth, and that they can be influenced by introducing other stimuli operating in other sensory systems (synesthesiae), further underscores the difference between the mechanism of LSD-produced brain phenomena and seizure phenomena. Occasionally, psychomotor epileptics, recognizing the threat on the basis of a sensory aura, may produce voluntarily a reflex counterstimulation, which, however, rather than changing the value of the sensory experience, merely terminates the aura, and, even so, not always.

The mood changes, which may vary from depression to elation in the same subject in the same experiment, may alternate from one to the other, along with such signs of emotional incontinence as seen in forced crying or forced laughter, suggest the activation of diencephalic circuits, possibly along the pathways of the two circuits for emotional expression originally described by Papez, although there may be many others.

These mood changes bring into mind the experimental findings by Foerster, Penfield, and Bailey, who were able to produce manic-like or depressive-like changes when mechanically stimulating the anterior or the posterior half of the floor of the third ventricle respectively.

The perceptual anomalies occurring in the somatosensory system, particularly those involving distortions and delusions of the body image, would implicate chiefly the postcentral parietal primary sensory receiving area, the surrounding associational strips, and the parietothalamic connections of the minor hemisphere, since most body-image distortions lateralized to that side.

The frequent complaints of numbness, particularly in the perioral area and in other midline structures, or the paresthesias prevailing in these same structures, are reminiscent of the sensory seizures, which are, in turn, localized to the secondary sensory receiving area.

In many cases a moderate defect in retention and immediate recall was noted, and it was also noteworthy that distortion occurred with respect to the correct appreciation of the duration component of time. There is a suspicion that the difficulty indicates interference with the recording element in the memory process, which, in turn, would suggest involvement of the amygdaloid complex. This structure may also be responsible for the reduction of sexual drive.

As mentioned under the heading of EEG changes, a marked increase in the average alpha perseveration time was observed in almost every instance. This means that, in response to a (visual) stimulus, the alpha blocking persisted for an inordinately long time. This finding has to be combined with another observation, namely, the markedly long persistence of the after-image, either positive or negative. Since here the occipital alpha rhythm is involved, there is reason to believe that the disturbance affects those cells responsible for occipital electrogenesis, and that some synaptic embarrassment is responsible for the prolonged alpha perseveration time and for the long persistence of the after-image.

The peculiarities of the LSD language, showing condensations of words, often of opposite meaning, suggest some conflict or confusion over twoness and an embarrassment over a choice. While this area has not been properly investigated, the similarity between these phenomena and what one commonly sees in schizophrenic states is not the least striking effect of the LSD psychosis.

A special chapter ought to be reserved to explain the modus operandi of the synesthesiae, especially because in a fair number of cases they occurred in a sequential order and so commonly ended by producing a paranoid state.

Ordinarily, sensory volleys travel in "closed conduits," even when the peripheral receptors of the various sense organs are simultaneously and maximally stimulated. Though collaterals reach such widely separated structures as the ascending reticular system in the brain stem, the hippocampus, and the cerebellum as the volley passes corticopetally, normally these impulses do not discharge into one another.

In the LSD state it was quite striking how often one form of stimulus influenced the perception of another form, suggesting some "cross-talk" mechanism between the individual sensory pathways. One can speculate about the level where this mutual penetration may take place. Sometimes the synesthesiae were quite primitive and quite simple, suggesting, in turn, that the confusion originates at a subcortical, for instance, a thalamic, level. A good example of this would be the disappearance of the illusion of angular-shaped designs and their instant metamorphosis to curved ones upon simply clapping the hands.

A far more complicated synesthesia, however, is the one in which the subject reports that his voice or his perceptual anomaly referable to the somatosensory system is influenced by the examiner's voice. Here, the correspondence, or, rather, abnormal correspondence, probably takes place on the cortical level between one sensory associational or recognition area and another, sensory primary receiving area, or its correspondent association and recognition components. In the most complicated instances, particularly when these sensory disturbances are associated with annoying emotional reactions, the frontal lobe and its connections both to the sensory associational areas lying more posteriorly and to the diencephalon will have to be implicated.

Another possibility is that the critical area is of one of cross talk in the hippocampus. Recent work indicates that the hippocampus is the recipient of afferent volleys coming in from all the sense organs, and it has earlier been established that the hippocampus is a very important link of the two primary emotional neuronal chains described by Papez. It is, therefore, conceivable that the distortion in sensory perception in the form of a synesthesia, entering in confusion in the form of afferent volleys into the hippocampus, may give rise to a strong discharge, which then will travel in the aforementioned two circuits of emotional expression, leading either to a fear or to anger or to both. Accordingly, the dysphoria of the paranoid state may originate at the hippocampal level.

Probing of the personality make-up of the subjects often furnished poorly reliable, and even contradictory, indices for the prediction of a subsequent paranoid reaction, so that the assumption gained momentum that the paranoid schizophrenic reaction need not be considered as a distortion of an underlying personality so inclined, but, rather, may be the outcome of a perceptual overload to which priority ought to be assigned in the hierarchy of stresses that an individual can tolerate. The delusional hallucinatory experiences of a paranoid nature induced by LSD enabled one to break this reaction down into its elements, study its evolution, as it were, "in slow motion," and observe the sequence of events leading up to the ultimate break.

Where general knowledge of the subject and the Rorschach test suggested confusion over sexual identification and repressed homosexuality, delusions of thought control and control over body sensations emanating from an examiner of the same sex could conceivably have set the stage for a homosexual panic or acted as precursors of a flight into a paranoid state to keep homosexuality from breaking into awareness. Paranoid inclination of male subjects was not interfered with when the examiner was of the opposite sex, though it must be stated that one of the women subjects (C) was always aware that she was under the direction of the senior author, of the male sex. Then, again, examined by the (male) senior author, three of the "paranoid" subjects were women.

There is an individual variation in frustration- and anxiety-tolerance, and such factors as individual sophistication might also explain this type of personality reaction to mental stress. It comes to mind, however, that experiments have been devised before in which the frustration- and stress-tolerances of individuals were put to severe test. For instance, subjects who speak into a microphone and then hear their voice through earphones with a certain amount of fixed delay describe the resultant confusion as being exceedingly unpleasant, at times leading to stuttering and to a great deal of anxiety, but we are not aware that a paranoid state resulted.

Considerations of dosage had to be discarded. Some of our subjects who developed paranoid reactions have taken only 0.5γ per kilogram, which is half of the average dose given by almost every author to their normal subjects.

In toxic-organic psychoses, especially when the state of consciousness is interfered with, the EEG shows signs of diffuse slowing, while in functional psychotic reactions no abnormalities are seen. In this respect, the LSD-induced psychotic state shows greater analogy with functional conditions, which would permit the speculation at least that both share the same substrate in the brain for which LSD shows the greatest affinity. On the other hand, least affected are those systems which form the core of the routine neurological examination and which utilize long tracts, such as the corticospinal, ascending sensory, and cerebello-extrapyramidal systems.

Many authors have emphasized the marked resistance of psychotic persons to such doses of LSD as are effective when given to normal subjects, though some observed such a resistance only in deteriorated cases.[9] This led some authors to assume that a LSD-like substance must already be present and in operation in psychotics; consequently, the addition of the infinitesimal amount which is effective in normal subjects, understandably, cannot possess any enhancing effect on the psychotic picture. As Condrau [13] has pointed out, the large doses merely increase the vegetative symptoms which set the limit of the amount of LSD anyone can tolerate. It is possible that in psychotics the same anatomicophysiological substrate that shows the greatest affinity for LSD is already involved; therefore, the resistance would be due to the fact that the substrate in question is already "busy" and, consequently, unable to react further to stimuli that are supposed to bear upon it by virtue of the circulating LSD. This explanation might be the same as that which would account for the common observation that psychotics rarely, if ever, change a psychosis, and that the development of one form of psychosis renders them "immune" to the development of another one. In this connection, an observation of Hoff and Arnold [45] may be pertinent. These authors have given LSD to patients with alcoholic psychosis. They have found that a great measure of resistance to LSD exists in subjects suffering from delirium tremens. In Korsakoff's syndrome, the reaction to LSD was the same as in normals so long as the midbrain and medulla were intact. In alcoholic psychoses, with more widespread damage (cortex, thalamus, hypothalamus, mammillary body, midbrain, and medulla), the LSD effect was nil. These data suggest that some structures in the diencephalon possess an LSD-sparing effect. Fabing[44] reported the LSD-antagonistic effect of the drug pipradrol, which, clinically, produces euphoria in depressed persons, and, therefore, one can assume that the point of its action is in the hypothalamus. Once again, therefore, it appears that if part of the critical substrate responsible for LSD psychosis is busy and under stimulation by another chemical, then LSD will not be able to dislodge or modify this effect and, therefore, some of the most important symptoms of LSD psychosis will not find expression.

Sketchy as the data so far available may be, they rather impressively point to a complex working mechanism. Interference with several enzyme systems would be one element of the LSD effect, and its selective embarrassment of that part of the central nervous system which subserves psychic function would be the other.

SUMMARY

d-Lysergic acid disthylamide (LSD-25) given to 25 normal adults produced widespread temporary alteration in psychic functioning which resembles most the undeteriorated schizophrenic reaction type.

Insight and detachment are sufficiently preserved to allow recognition of the split between thinking and feeling as reality control becomes disturbed.

Rorschach tests completed in 13 cases allowed a fairly good prediction of a psychotic-like change from the control to the drug test, though the type of model psychosis could not be reliably anticipated.

Paranoid-like reaction (14 cases) showed a better correlation with the occurrence of complex synesthesiae, especially when the cross influence involved the examiner's voice and thoughts, on the one hand, and the subject's thoughts and bodily sensations, on the other.

Theories aiming at elucidating the working mechanism of this drug point toward enzyme inhibition, on the biochemical side, and predominant vulnerability of the temporal lobe-diencephalic circuits, on the neurophysiological side.

450 N. Bedford Dr.

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